Free, Donna

From: Free, Donna
Sent: Thursday, November 11, 2004 11:25 AM
To: 'Allen, Samie Niver'
Cc: Hanafi, Nada O; Michael, Maher
Subject: RE: P030053a5 - modes and causes of rupture

HI Samie,

Attached please find our responses to the questions regarding modes and causes of rupture you posed on 11/4/04. We hope that this response adequately responds to your questions. Please let us know if you need any additional information regarding this important topic.

Have a nice day off.

Regards,

Donna

-----Original Message-----
From: Allen, Samie Niver [mailto:SXN@CDRH.FDA.GOV]
Sent: Thursday, November 04, 2004 3:12 AM
To: 'Free, Donna'
Cc: Michael, Maher; Hanafi, Nada O
Subject: P030053a5 - modes and causes of rupture

Donna,
I just discovered that I failed to send out this email yesterday. Sorry.

1. In your 10/28/04 email, you show only 110 iatrogenic failures. However, Attachment 5 on p.2030 shows 508 iatrogenic failures with in-vivo times. Please explain the reasons for the discrepancy.

2. In your 10/28/04 email, you stated that you believed that the fatigue testing life of 60 years is excessively high. You then stated that the "laboratory cyclic fatigue testing represents a reasonable *in vitro* simulation of the long term fatigue failure of devices *in vivo*. The problem that leads to what we believe is a high lifetime estimate is most likely the model that translates the laboratory test results into an estimate for *in vivo* failure. Nevertheless, on a qualitative basis, it can be safely assumed that the time to overt failure for devices surviving beyond 15 years will be long." Your statement seems to be contradictory and I do not understand it. Please clarify what extent you believe the fatigue bench testing plays in predicating in-vivo cycles to failure. This is an important clarification because it plays into the value of your Attachment 11 testing.

1. In your 10/28/04 email, you show only 110 iatrogenic failures. However, Attachment 5 on p.2030 shows 508 iatrogenic failures with in-vivo times. Please explain the reasons for the discrepancy.

1 Response:

The 508 iatrogenic failures shown on page 2030 of Attachment 5 are the **total worldwide** complaints in the Iatrogenic (User Related) category with known *in vivo* time. The 110 iatrogenic failures are a subset of the total----- devices categorized as such. They are the devices with domestic (U. S.) complaints with a known *in vivo* time that were used for evaluation in the Barber report in Attachment 5. The table below shows the relationship between the worldwide and domestic U. S. complaints.

Iatrogenic (User Related) Complaints

	Worldwide		Domestic U. S.	
	Number	**Percent**	**Number**	**Percent**
Total population of complaints	----		171*	
No abnormality	---	------	1	0.6%
In vivo time unknown	----	-------	60	35.1%
Population remaining for analysis	----	-------	**110**	64.3%

* Includes devices for which "rupture," "leaking," "defective" or "tear/hole" were reported as the primary complaint. Devices with reported "capsular contracture," "breast pain," "asymmetry," "auto-immune," "hematoma," implant displacement," "infection," "silicone fear," "wrinkle," "wrong size" or "inflammation." (a total of 37 devices) as the primary complaint were excluded. The reason for this exclusion was to ensure that the devices included in the sample had the highest probability of failing from user-related actions. If these exclusory categories had not been applied, the total sample would have been 208.

2. In your 10/28/04 email, you stated that you believed that the fatigue testing life of 60 years is excessively high. You then stated that the "laboratory cyclic fatigue testing represents a reasonable in vitro simulation of the long term fatigue failure of devices in vivo. The problem that leads to what we believe is a high lifetime estimate is most likely the model that translates the laboratory test results into an estimate for in vivo failure. Nevertheless, on a qualitative basis, it can be safely assumed that the time to overt failure for devices surviving beyond 15 years will be long." Your statement seems to be contradictory and I do not understand it. Please clarify what extent you believe the fatigue bench testing plays in predicating in-vivo cycles to failure. This is an important clarification because it plays into the value of your Attachment 11 testing.

2 Response:

Mentor is highly confident that cyclic fatigue testing provides a sound *in vitro* simulation of the long term fatigue failure of devices *in vivo*. There are a few reasons why this mechanical testing provides a sound basis for predicting device life: It is not confounded

with other modes of failure, such as, localized shell stress, sharp instrument cuts or punctures or localized shell fatigue. This means that the results from testing will be predictive strictly of cyclic fatigue failures. The frequency of short term failures reach a maximum value between 5 and 9 years *in vivo* and then diminish to a negligible rate after about 15 years. These short term failures involve several modes of failure and have already been characterized and documented in the analysis of explanted returned product. Failures that occur up to 15 years *in vivo* account for only a small percentage of the total population of implants. It is our opinion, and stated in our response dated 10/28/04, that long term cyclic fatigue failure is likely to be the prominent mode for the eventual failure of the remainder of the population.

Predicting device life based upon cyclic fatigue date requires three elements: (1) cyclic fatigue tests conducted at constant stress and carried out to device failure, (2) a relationship (Basquin-Gerber equation) that provides a correlation between the laboratory fatigue data and *in vivo* device life and (3) model assumptions of *in vivo* conditions that are assumed to lead to failure. These are each discussed separately in the following paragraphs.

The cyclic fatigue testing conducted in the Mentor laboratories is specifically designed to determine long term fatigue life. The testing stresses the area that is most vulnerable to failure, the radius area. The examination of failed products and analysis of the results of those examinations have demonstrated that the radius is the region on the device most susceptible to failure.[1] Test conditions simulate the *in vivo* environment. The tests are conducted at conditions that produce a failure within a time span that provides failure data in a practical length of time: Load amplitude of ~20-80 lb_f and frequency of 1 Hz. Based upon all of the above observations, it is reasonable to conclude that laboratory cyclic fatigue testing as conducted by Mentor will provide a sound basis for predicting device life.

The Basquin-Gerber equation is widely accepted as the tool for predicting fatigue failures of elastomers. This is the relationship that Mentor used to project device life. Substitution of cyclic fatigue test data that includes cycles to failure and corresponding stress at which the test was conducted into the Basquin-Gerber equation provide parameters that are directly applicable to Mentor implants. The substitution of these derived parameters into the equation along with model assumptions about *in vivo* stresses and frequency of stress allows the calculation of device life.

The selection of model assumptions is critical to the calculated device life. The assumptions that we made in our determination of device life are that an average size woman with breast implants will walk or jog for 8 hours a day and that partial folds are produced at the frequency of (1 Hz) during that activity. This folding, or wrinkling, will produce ~15% strain with a corresponding stress of 20 lb_f. <u>These model assumptions produce a range of device lives with a minimum of 60 years</u>. The specific *in vivo* model that we selected for use was conservative and was based upon a model that produced the shortest device life.

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[1] Barber, JR. *An Investigation of the Modes and Causes of Failure of Gel-Filled Breast Implant Devices in the Rent-Unknown Cause" and "Not Apparent-Etiology Unknown" Categories of the Product Evaluation Database*, Attachment 5 to the Response to the FDA Deficiency Letter dated April 11, 2004.

It should be noted that other model assumptions, such as, embracing a number of times per day, a very large woman sleeping on her stomach for 8 hours, etc., were used in conjunction with the model assumptions from the previous sentence to calculate device life. None of these resulted in a significantly reduced device life and were excluded from the final, selected model (walking or jogging with a wrinkling causing a repetitive strain of ~15%).

In summary, Mentor strongly believes that the cyclic fatigue testing does accurately reproduce the long term fatigue failure mode of a device. This long term mode of failure will emerge after the short term failures that occur up to about 15 years. The Basquin-Gerber has been used widely to determine long term failures of elastomers under cyclic fatigue and its use in the determination of the life of breast implants is appropriate. The actual *in vivo* conditions (frequency and stress) used to calculate the lifetime are selected based on likely or reasonable activities of an implanted patient and the resultant frequency of and stress on the device created by those activities. As previously stated, the specific *in vivo* model that we selected for use in determining device was based upon a model that produced the shortest device life.

A lower lifetime may result if other factors could be identified, verified and used in the Basquin-Gerber equation to calculate a lower lifetime. We indeed attempted to develop models that would lower the device life, however, we were unable to develop a reasonable model. The model for the 60-year life projection depends upon observable activities of a patient (walking or jogging at a given frequency and with the resultant stress).

One possibility for reducing the device life is that unobservable events could be contributing factors to failures. For example, normal flexing of the pectoralis major muscle may influence time to failure, especially in women that have submuscular placement of the device. In this case, each time the pectoralis major muscle contracts, it will stress the implanted device. The frequency of application of this stress on the device would most likely far exceed the frequency of stress of ~8 hours of walking or jogging that was assumed in our original model. The associated stress would probably be much less than included in that model (20 lb_f) and this added factor would probably increase the predicted life of the device. The difficulty in adding such a factor into the estimation of device life is that the frequency of the flexing of the muscle is extremely difficult to determine and, undoubtedly, is a very strong function of the individual patient. In addition, it would be almost impossible to measure the stress induced on a device as the result of muscle flexing. Furthermore, the resultant stress is most likely so low that the calculated life of a device based strictly upon this model would be much greater than 60 years. The point of this example was to demonstrate that there may possibly be other factors that influence device life that simply have not been identified although we believe that this is unlikely.

When we made the point in the 10/28/04 response that the 60 years could be an excessively long life, we were merely recognizing the possibility that there might be some other model parameters that could be utilized in conjunction with the existing laboratory cyclic fatigue data and the Basquin-Gerber relationship that we had not identified that could lead to a shorter device life. We have tried diligently to identify a challenging, but realistic, model on which to base the calculation of device life. We were

merely attempting to point out that failures may develop in the future from some unanticipated cause, such as the one that was hypothesized in the previous paragraph, that could produce a lower device life. We have not identified any practical model conditions that are more challenging than the ones that we chose and that produced the average device life of 60 years.

It must be emphasized here that we were not questioning the validity of the fatigue testing *per se* nor the use of the Basquin-Gerber in determining the device life. We are convinced that both are technically sound. The point that we were trying to make is that there is the possibility, no matter how small, that other model assumptions could lead to a shorter device life. Since we could not identify any such conditions or assumptions, we reverted to simple logic to establish an estimate of the very lowest possible median life of 25 years and assumed that the failure rate at 15 years (16% failures in 15 years) would continue and be constant to provide an upper limit of a median life of 47 years. These limiting extrapolations were presented to emphasize that, even when the absolute worst case generalized assumptions are applied, the median life of these devices is substantial.

In conclusion, Mentor is highly confident that cyclic fatigue testing provides a sound *in vitro* simulation in predicating in-vivo cycles to failure.